

Claims:

1. A dosage form of combination of high dose high solubility active ingredient, as modified release and low dose active ingredient as immediate release suitable for swallowing; comprising of dual retard technique to control the release of high dose,
5 high solubility active ingredient, wherein said dosage form comprising of an inner portion having a low dose active ingredient as immediate release and an outer portion having a high dose, high solubility active ingredient as modified release, in which the outer portion comprises a) micro matrix particles and b) coating on micro matrix
10 particles.
2. A dosage form according to claim 1, in the form of a tablet, wherein said inner portion is covered by the outer portion from all the sides except top surface that remains uncovered.
3. A dosage form according to claim 1, wherein the dosage form is with sufficient
15 reduction in the amount of release controlling agent.
4. A dosage form according to claim 1, wherein the micro matrix particles comprises one or more hydrophobic release controlling agents.
5. A dosage form according to claim 4, wherein the hydrophobic release controlling agents are selected from the group comprising of ammonio methacrylate copolymers
20 type A and B as described in USP, methacrylic acid copolymer type A, B and C as described in USP, polyacrylate dispersion 30% as described in Ph. Eur., polyvinyl acetate dispersion, ethylcellulose, cellulose acetate, cellulose propionate (lower, medium or higher molecular weight), cellulose acetate propionate, cellulose acetate butyrate, cellulose acetate phthalate, cellulose triacetate, poly(methyl methacrylate),
25 poly(ethyl methacrylate), poly(butyl methacrylate), poly(isobutyl methacrylate), poly(hexyl methacrylate), poly(isodecyl methacrylate), poly(lauryl methacrylate), poly(phenyl methacrylate), poly(methyl acrylate), poly(isopropyl acrylate), poly(isobutyl actylate), poly(octadecyl acrylate), waxes such as beeswax, carnauba wax, microcrystalline wax, and ozokerite; fatty alcohols such as cetostearyl alcohol, stearyl alcohol; cetyl alcohol and myristyl alcohol; and fatty acid esters such as glyceryl
30 monostearate, glycerol distearate, glycerol monooleate, acetylated monoglycerides, tristearin, tripalmitin, cetyl esters wax, glyceryl palmitostearate, glyceryl behenate and hydrogenated castor oil.

6. A dosage form according to claim 5, wherein the hydrophobic release controlling agent(s) is selected preferably from ammonio methacrylate co-polymers.
7. A dosage form according to claim 6, wherein the preferred ammonio methacrylate co-polymers are selected from Eudragit RSPO (Ammonio Methacrylate Copolymer type B USP), Eudragit RL (Ammonio Methacrylate Copolymer type A USP) and Eudragit NE30D (Polyacrylate dispersion 30% Ph. Eur.).
8. A dosage form according to claim 1, wherein in micro matrix particles, the active ingredient and one or more hydrophobic release controlling agents are present in a ratio of from 100:1 to 100:75.
9. A dosage form according to claim 8, wherein in micro matrix particles, the active ingredient and one or more hydrophobic release controlling agents are present preferably in ratio of from 100:2.5 to 100:50.
10. A dosage form according to claim 8, wherein in micro matrix particles, the active ingredient and one or more hydrophobic release controlling agents are present more preferably in ratio of from 100:2.5 to 100:30.
11. A dosage form according to claim 8, wherein in micro matrix particles, the active ingredient and one or more hydrophobic release controlling agents are present most preferably in ratio of from 100:2.5 to 100:20.
12. A dosage form according to claim 1, coating of micro matrix particles comprises one or more hydrophobic release controlling agents.
13. A dosage form according to claim 12, wherein the hydrophobic release controlling agents are selected from the group comprising of ammonio methacrylate copolymers type A and B as described in USP, methacrylic acid copolymer type A, B and C as described in USP, polyacrylate dispersion 30% as described in Ph. Eur., polyvinyl acetate dispersion, ethylcellulose, cellulose acetate, cellulose propionate (lower, medium or higher molecular weight), cellulose acetate propionate, cellulose acetate butyrate, cellulose acetate phthalate, cellulose triacetate, poly(methyl methacrylate), poly(ethyl methacrylate), poly(butyl methacrylate), poly(isobutyl methacrylate), poly(hexyl methacrylate), poly(isodecyl methacrylate), poly(lauryl methacrylate), poly(phenyl methacrylate), poly(methyl acrylate), poly(isopropyl acrylate), poly(isobutyl acrylate), poly(octadecyl acrylate), waxes such as beeswax, carnauba wax, microcrystalline wax, and ozokerite; fatty alcohols such as cetostearyl alcohol, stearyl alcohol; cetyl alcohol and myristyl alcohol; and fatty acid esters such as glyceryl monostearate, glycerol distearate, glycerol monooleate, acetylated monoglycerides,

tristearin, tripalmitin, cetyl esters wax, glyceryl palmitostearate, glyceryl behenate glycerol distearate, and hydrogenated castor oil.

14. A dosage form according to claim 13, wherein the hydrophobic release controlling agent(s) is selected from fatty acid esters.
- 5 15. A dosage form according to claim 14, wherein the hydrophobic release controlling agents is selected from the group comprising of hydrogenated castor oil and glycerol distearate.
16. A dosage form according to claim 1, wherein in outer portion, micro matrix particles and coating of one or more hydrophobic release controlling agents are present in a
10 ratio of from 100:0.5 to 100:75.
17. A dosage form according to claim 16, wherein in outer portion, micro matrix particles and coating of one or more hydrophobic release controlling agents are present preferably in a ratio of from 100:1 to 100:50.
18. A dosage form according to claim 16, wherein in outer portion, micro matrix particles
15 and coating of one or more hydrophobic release controlling agents are more preferably present in a ratio of from 100:2.5 to 100:20.
19. A dosage form according to claim 1, wherein the weight ratio of immediate release active ingredient and modified release active ingredient is from 1:10 to 1:15000.
20. A dosage form according to claim 1, wherein the low dose active ingredient
20 comprises dose less than or equal to 50 mg.
21. A dosage form according to claim 1, wherein the low dose active ingredient is selected from the group comprising of antidiabetic agents, anti-histamines, anti-depressants, anti-viral agents, anesthetics, antacids, anti-arththriics, antibiotics, anti-
25 psychotics, anti-spasmodics, anxiolytic agents, appetite suppressants, cardiovascular agents, cough suppressants, emollients, gastro-intestinal agents, growth regulators, respiratory stimulants, vitamins, angiotensin converting enzyme inhibitors, anti-asthmatics, anti-cholesterolemics, anti-convulsants, anti-depressants, anti-diarrhea preparations, anti-infective, anti-inflammatory agents, anti-nauseants, anti-stroke agents, anti-tumor drugs, anti-tussives, anti-uricemic drugs, amino-acid preparations, antiemetics, antiobesity drugs, antiparasitics, antipyretics, appetite stimulants,
30 cerebral dilators, chelating agents, cholecystokinin antagonists, cognition activators, deodorants, dermatological agents, diuretics, erythropoietic drugs, fertility agents, synthetic hormones, laxatives, mineral supplements, neuroleptics, neuromuscular agents, peripheral vaso-dilators, prostaglandins, vaginal preparations, vaso-

constrictors, vertigo agents, sulphonylurease, meglitinides, PPAR gama agonist [insulin sensitisers (thiazolidinedione)], PPAR alpha and gamma agonist, alpha-glucosidase inhibitors and the like.

22. A dosage form according to claim 21, wherein the low dose active ingredient is selected from the group comprising of zafirlukast, quinapril hydrochloride, isotretinoin, rabeprazole sodium, estradiol(e2), norethindrone acetate, risedronate sodium, pioglitazone HCl, amphetamine, anagrelide hydrochloride, biperiden HCl, mephalan, alprazolam, ramipril, naratriptan hydrochloride, leflunomide, anastrozole, exemestane, paroxetine mesylate, candesartan cilexetil, almotriptan, cerivastatin, betaxolol hydrochloride, bisoprolol fumarate, deloratadine, clonazepam, clorazepate dipotassium, clozapine, methylphenidate hci, carvedilol, warfarin sodium, norgestrel, ethinyl estradiol, cyclophosphamide, pemoline, liothyronine sodium, misoprostol, tolterodine tartrate, dextroamphetamine sulfate, dicyclomine hydrochloride, digoxin, oxybutynin chloride, doxazosin mesylate, ethacrynate sodium, venlafaxine HCl, enalapril maleate, estradiol, estropipate, famotidine, letrozole, fludrocortisone acetate, fluoxetine, dexmethylphenidate hci, alendronate sodium, ziprasidone, glipizide, glyburide, miglitol, guanabenz acetate, haloperidol, doxercalciferol, zalcitabine, hydrochlorothiazide, hydromorphone HCl, indapamide, estradiol, nitric oxide, ketorolac tromethamine, clonazepam, granisetron, lamotrigine, fluvastatin sodium, levonorgestrel, levothyroxine sodium, atorvastatin calcium, lisinopril, minoxidil, loperamide, loratidine, lorazepam, lovastatin, pravastatin sodium, fluvoxamine maleate, acetaminophen, acyclovir, aminocaproic acid, pitavastatin, rosuvastatin, dalvastatin, escitalopram, sertraline, celecoxib, parecoxib, valdecoxib, glibenclamide (glyburide), glipizide, gliclazide, glimepiride, tolazamide, tolbutamide, clorpropamide, gliquidone, nateglinide, glyburide, glisoxepid, glibornuride, phenbutamide, tolcyclamide, repaglinide, troglitazone, ciglitazone, pioglitazone, englitazone, acarbose, voglibose, emiglitate, miglitol, farglitazar, (S)-2-ethoxy-3-[4-(2-{4-methanesulfonyloxyphenyl}ethoxy)phenyl]propanoic acid, 3-{4-[2-(4-tert-butoxycarbonylamino)phenyl]ethoxy}phenyl)-(S)-2-ethoxy propanoic acid, L-6766892 and pharmaceutically acceptable salts thereof.
23. A dosage form according to claim 1, wherein the high dose, high solubility active ingredient comprises dose from 500 mg to 1500 mg.
24. A dosage form according to claim 1, wherein the high dose, high solubility active ingredient is selected from the group comprising of antidiabetic agents, anti-

- histamines, anti-depressants, anti-viral agents, anesthetics, antacids, anti-arththriics, antibiotics, anti-psychotics, anti-spasmodics, anxiolytic agents, appetite suppressants, cardiovascular agents, cough suppressants, emollients, gastro-intestinal agents, growth regulators, respiratory stimulants, vitamins, angiotensin converting enzyme inhibitors, anti-asthmatics, anti-cholesterolemics, anti-convulsants, anti-depressants, anti-diarrhea preparations, anti-infective, anti-inflammatory agents, anti-nauseants, anti-stroke agents, anti-tumor drugs, anti-tussives, anti-uricemic drugs, amino-acid preparations, antiemetics, antiobesity drugs, antiparasitics, antipyretics, appetite stimulants, cerebral dilators, chelating agents, cholecystokinin antagonists, cognition activators, deodorants, dermatological agents, diuretics, erythropoietic drugs, fertility agents, synthetic hormones, laxatives, mineral supplements, neuroleptics, neuromuscular agents, peripheral vaso-dilators, prostaglandins, vaginal preparations, vaso-constrictors, biguanides, vertigo agents and the like.
25. A dosage form according to claim 1, wherein the high dose, high solubility active ingredient is selected from the group comprising of metformin hydrochloride, phenformin, buformin, potassium chloride, clindamycin, hydroxyurea, erythromycin, lactobionate, vancomycin hydrochloride, balsalazide disodium, sodium valproate, niacin, aminocaproic acid, acetaminophen ciprofloxacin, quetiapine and pharmaceutically acceptable salts thereof.
26. A dosage form according to claim 1, wherein inner portion may optionally contain more than one low dose active ingredients.
27. A dosage form according to claim 1, wherein the dissolution of high dose, high solubility active ingredient is not more than 45% in 1 hour and between 25% to 90% in 6 hours.
28. A dosage form according to claim 1, wherein the dosage form can be given twice a day or more preferably can be given once a day oral formulation.
29. A dosage form according to claim 1, is used for human beings.
30. A process for the preparation of a dosage form comprising a) preparation of inner portion and b) preparation of outer portion.
31. A process for the preparation of a dosage form as claimed in claim 30, wherein preparation of outer portion comprising a) preparing a micro matrix particles containing high dose, high solubility active ingredient and one or more hydrophobic release controlling agent and b) coating the said micro matrix particles containing

high solubility active ingredient and one or more hydrophobic release controlling agent.

32. A dosage form according to claim 1, wherein outer portion may optionally contain more than one high dose high solubility active ingredients.
- 5 33. A dosage form of combination of high dose high solubility antidiabetic active ingredient is as modified release and low dose antidiabetic active ingredient as immediate release, suitable for swallowing; comprising of dual retard technique to control the release of the high dose high solubility antidiabetic active ingredient wherein said dosage form comprising of an inner portion having a low dose
10 antidiabetic active ingredient as immediate release and an outer portion having a high dose high solubility antidiabetic active ingredient as modified release, in which the outer portion comprises a) micro matrix particles and b) coating on micro matrix particles.
- 15 34. A dosage form according to claim 33, which is a tablet, in which the inner portion is covered by the outer portion from all the sides except top surface that remains uncovered.
35. A dosage form according to claim 33, wherein the dosage form is with sufficient reduction in the amount of release controlling agent.
- 20 36. A dosage form according to claim 33, wherein the micro matrix particles comprises one or more hydrophobic release controlling agents.
- 25 37. A dosage form according to claim 36, wherein the hydrophobic release controlling agents are selected from the group comprising of ammonio methacrylate copolymers type A and B as described in USP, methacrylic acid copolymer type A, B and C as described in USP, polyacrylate dispersion 30% as described in Ph. Eur., polyvinyl acetate dispersion, ethylcellulose, cellulose acetate, cellulose propionate (lower, medium or higher molecular weight), cellulose acetate propionate, cellulose acetate butyrate, cellulose acetate phthalate, cellulose triacetate, poly(methyl methacrylate), poly(ethyl methacrylate), poly(butyl methacrylate), poly(isobutyl methacrylate), poly(hexyl methacrylate), poly(isodecyl methacrylate), poly(lauryl methacrylate),
30 poly(phenyl methacrylate), poly(methyl acrylate), poly(isopropyl acrylate), poly(isobutyl acrylate), poly(octadecyl acrylate), waxes such as beeswax, carnauba wax, microcrystalline wax, and ozokerite; fatty alcohols such as cetostearyl alcohol, stearyl alcohol; cetyl alcohol and myristyl alcohol; and fatty acid esters such as glyceryl monostearate; glycerol monooleate, acetylated monoglycerides, tristearin,

tripalmitin, cetyl esters wax, glyceryl palmitostearate, glyceryl behenate, glycerol distearate and hydrogenated castor oil.

38. A dosage form according to claim 37, wherein the hydrophobic release controlling agent(s) is selected preferably from ammonio methacrylate co-polymers.
- 5 39. A dosage form according to claim 38, wherein the preferred ammonio methacrylate co-polymers are selected from Eudragit RSPO (Ammonio Methacrylate Copolymer type B USP), Eudragit RL (Ammonio Methacrylate Copolymer type A USP) and Eudragit NE30D (Polyacrylate dispersion 30% Ph. Eur.).
40. A dosage form according to claim 33, wherein in micro matrix particles, the
10 antidiabetic active ingredient and one or more hydrophobic release controlling agents are present in a ratio of from 100:1 to 100:75.
41. A dosage form according to claim 40, wherein in micro matrix particles, the antidiabetic active ingredient and one or more hydrophobic release controlling agents are present preferably in ratio of from 100:2.5 to 100:50.
- 15 42. A dosage form according to claim 40, wherein in micro matrix particles, the antidiabetic active ingredient and one or more hydrophobic release controlling agents are present more preferably in ratio of from 100:2.5 to 100:30
43. A dosage form according to claim 40, wherein in micro matrix particles, the antidiabetic active ingredient and one or more hydrophobic release controlling agents
20 are present most preferably in ratio of from 100:2.5 to 100:20.
44. A dosage form according to claim 33, wherein coating of micro matrix particles comprises one or more hydrophobic release controlling agents.
45. A dosage form according to claim 44, wherein the hydrophobic release controlling agents are selected from the group comprising of ammonio methacrylate copolymers
25 type A and B as described in USP, methacrylic acid copolymer type A, B and C as described in USP, polyacrylate dispersion 30% as described in Ph. Eur., polyvinyl acetate dispersion, ethylcellulose, cellulose acetate, cellulose propionate (lower, medium or higher molecular weight), cellulose acetate propionate, cellulose acetate butyrate, cellulose acetate phthalate, cellulose triacetate, poly(methyl methacrylate),
30 poly(ethyl methacrylate), poly(butyl methacrylate), poly(isobutyl methacrylate), poly(hexyl methacrylate), poly(isodecyl methacrylate), poly(lauryl methacrylate), poly(phenyl methacrylate), poly(methyl acrylate), poly(isopropyl acrylate), poly(isobutyl acrylate), poly(octadecyl acrylate), waxes such as beeswax, carnauba wax, microcrystalline wax, and ozokerite; fatty alcohols such as cetostearyl alcohol,

stearyl alcohol; cetyl alcohol and myristyl alcohol; and fatty acid esters such as glyceryl monostearate; glycerol monooleate, acetylated monoglycerides, tristearin, tripalmitin, cetyl esters wax, glyceryl palmitostearate, glyceryl behenate, glycerol distearate and hydrogenated castor oil.

- 5 46. A dosage form according to claim 45, wherein the hydrophobic release controlling agent(s) is selected from fatty acid esters.
47. A dosage form according to claim 46, wherein the hydrophobic release controlling agents are selected from the group comprising of hydrogenated castor oil and glycerol distearate.
- 10 48. A dosage form according to claim 33, wherein in outer portion, micro matrix particles and coating of one or more hydrophobic release controlling agents are present in a ratio of from 100:0.5 to 100:75.
49. A dosage form according to claim 48, wherein in outer portion, micro matrix particles and coating of one or more hydrophobic release controlling agents are present preferably in a ratio of from 100:1 to 100:50.
- 15 50. A dosage form according to claim 48, wherein in outer portion, micro matrix particles and coating of one or more hydrophobic release controlling agents are more preferably present in a ratio of from 100:2.5 to 100:20.
51. A dosage form according to claim 33, wherein the weight ratio of immediate release antidiabetic active ingredient and modified release antidiabetic active ingredient is from 1:10 to 1:15000
- 20 52. A dosage form according to claim 33, wherein the low dose antidiabetic active ingredient comprises dose less than or equal to 50 mg.
53. A dosage form according to claim 33, wherein the low dose antidiabetic active ingredient is selected from the group comprising of sulphonylurease, meglitinides, PPAR gamma agonist [insulin sensitisers (thiazolidinedione)], alpha-glucosidase inhibitors, PPAR alpha and gamma agonist.
- 25 54. A dosage form according to claim 33, wherein the low dose antidiabetic active ingredient is selected from the group comprising of glibenclamide (glyburide), glipizide, glimepiride, tolazamide, tolbutamide, clorpropamide, glimepiride, nateglinide, glyburide, glisoxepid, glibornuride, phenbutamide, tolcyclamide, repaglinide, troglitazone, ciglitazone, pioglitazone, englitazone, acarbose, voglibose, emiglitazone, miglitol, farglitazar, (S)-2-ethoxy-3-[4-(2-{4-methanesulfonyloxyphenyl}ethoxy)phenyl]propanoic acid, 3-{4-[2-(4-tert-
- 30

butoxycarbonylaminophenyl) ethoxy]phenyl)-(S)-2-ethoxy propanoic acid and pharmaceutically acceptable salts thereof.

55. A dosage form according to claim 33, wherein the high dose high solubility antidiabetic active ingredient is selected from biguanides.
56. A dosage form according to claim 33, wherein the high dose high solubility antidiabetic active ingredient is selected from the group comprising of metformin hydrochloride, phenformin and buformin
57. A dosage form according to claim 33, wherein the high dose high solubility antidiabetic active ingredient comprises dose from 500 mg to 1500 mg.
58. A dosage form according to claim 33, is once a day oral formulation.
59. A dosage form according to claim 33, is used for human beings.
60. A dosage form according to claim 33, wherein the high dose high solubility antidiabetic active ingredient is metformin hydrochloride.
61. A dosage form according to claim 33, wherein the composition of outer portion is as follows-

Micro matrix particles-

Metformin hydrochloride	75%w/w to 99%w/w
Eudragit RS	1%w/w to 25%w/w

Coated micro matrix particles

Micro matrix particles	70%w/w to 99%w/w
Hydrogenated castor oil	1%w/w to 30%w/w
Magnesium stearate	0%w/w to 2%w/w

62. A dosage form according to claim 33, wherein the dissolution of metformin hydrochloride is not more than 50% in one hour, from 30 to 90 % in four hours and not less than 65 % in twelve hours.
63. A dosage form according to claim 33, wherein the maximum plasma metformin concentration is achieved between 700 ng/ml and 2500 ng/ml.
64. A dosage form according to claim 33, wherein the maximum plasma metformin concentration is achieved preferably between 900 ng/ml and 2400 ng/ml.
65. A dosage form according to claim 33, wherein the maximum plasma metformin concentration is achieved more preferably between 1000 ng/ml and 2350 ng/ml.

66. A dosage form according to claim 33, wherein the modified release metformin hydrochloride formulations for once daily administration exhibit *in vivo* mean dissolution time (MDT) of 4 hours to 6 hours.
67. A dosage form according to claim 33, wherein the minimum plasma metformin concentration (at 24 hours) ranges between 0 and 450 ng/ml after oral administration.
68. A dosage form according to claim 33, wherein the low dose antidiabetic active ingredient is rosiglitazone maleate.
69. A dosage form according to claim 33, wherein the low dose antidiabetic active ingredient is glimepiride.
70. A dosage form as claimed in claim 60 and 68, wherein the bioavailability of rosiglitazone is not affected when it is coadministered with metformin hydrochloride.
71. A dosage form according to claim 33, wherein inner portion may optionally contain more than one antidiabetic active ingredients.
72. A dosage form according to claim 33, wherein outer portion may optionally contain more than one antidiabetic active ingredients.
73. A process for the preparation of a dosage form as claimed in claim 33, comprising a) preparation of inner portion and b) preparation of outer portion.
74. A process for the preparation of a dosage form as claimed in claim 73, wherein preparation of outer portion comprising a) preparing a micro matrix particles containing high dose, antidiabetic active ingredient and one or more hydrophobic release controlling agent and b) coating the said micro matrix particles containing high dose antidiabetic active ingredient and one or more hydrophobic release controlling agent.

**This Page is Inserted by IFW Indexing and Scanning
Operations and is not part of the Official Record**

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

☐ **BLACK BORDERS**

☐ **IMAGE CUT OFF AT TOP, BOTTOM OR SIDES**

☐ **FADED TEXT OR DRAWING**

☒ **BLURRED OR ILLEGIBLE TEXT OR DRAWING**

☐ **SKEWED/SLANTED IMAGES**

☐ **COLOR OR BLACK AND WHITE PHOTOGRAPHS**

☐ **GRAY SCALE DOCUMENTS**

☐ **LINES OR MARKS ON ORIGINAL DOCUMENT**

☐ **REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY**

☐ **OTHER:** _____

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.